CLAIMS

What is claimed is:

1. A method for identifying compounds binding to PYK2, comprising

determining the orientation of at least one compound bound with PYK2 in co-crystals of PYK2 with said compound.

2. The method of claim 1, wherein said compound is identified as a molecular scaffold if it binds weakly to PYK2 and has a molecular weight less than 350 daltons.

3. The method of claim 2, wherein said method further comprises identifying chemical structures of said molecular scaffolds, that, when modified, alter the binding affinity or binding specificity or both between the molecular scaffold and PYK2.

4. The method of claim 3, wherein further comprising synthesizing a ligand wherein one or more of the chemical structures of the molecular scaffold is modified to provide a ligand that binds to PYK2 with altered binding affinity or binding specificity or both.

5. The method of claim 2, wherein said molecular scaffold binds to a plurality of kinases.

6. The method of claim 2, wherein said molecular scaffold interacts with one or more of PYK2 residues 503, 505, 457, 488, 567, and 554.

7. The method of claim 4, wherein said ligand has a chemical structure of Formula

8. A method for obtaining improved ligands binding to PYK2, comprising

identifying a compound that binds to PYK2 and determining whether said compound interacts with one or more of PYK2 residues 503, 505, 457, 488, 567, and 554;

determining whether a derivative of said compound binds to PYK2 with greater affinity or greater specificity or both than said compound, wherein binding with greater affinity or greater specificity or both indicates that said derivative is an improved ligand.

9. The method of claim 8, wherein said derivative has at least 10-fold greater affinity or specificity or both than said compound.

10. The method of claim 8, wherein said derivative has at least 100-fold greater affinity or specificity or both.

11. The method of claim 8, wherein said compound has a chemical structure of Formula I.

12. A method for developing ligands specific for PYK2, comprising

identifying a compound that binds to a plurality of kinases; and

determining whether a derivative of said compound has greater specificity for PYK2 than said compound.

13. The method of claim 12, wherein said compound binds to PYK2 with an affinity at least 10-fold greater than for binding to any of said plurality of kinases.

14. The method of claim 12, wherein said compound interacts with at least one of PYK2 residues residues 503, 505, 457, 488, 567, and 554.

15. The method of claim 12, wherein said compound is a compound of Formula I.

16. The method of claim 12, wherein said compound binds weakly to said plurality of kinases.

17. A crystalline form of PYK2 kinase domain.

18. The crystalline form of claim 17, having coordinates as described in Table 1.

19. The crystalline form of claim 17, comprising one more more heavy metal atoms.

20. The crystalline form of claim 17, wherein said crystalline form comprises a co-crystal of PYK2 with a binding compound.

21. The crystalline form of claim 20, wherein said binding compound interacts with one or more of PYK2 residues 503, 505, 457, 488, 567, and 554.

22. The crystalline form of claim 17, wherein said crystalline form is in an X-ray beam.

23. The crystalline form of claim 17, wherein said PYK2 is mutated.

24. A method for obtaining a crystal of PYK2, comprising subjecting PYK2 protein at 5-20 mg/ml to crystallization condition substantially equivalent to 2-10 % polyethylene glycol (PEG) 8000, 0.2 M sodium acetate, 0.1% sodium cacodylate pH 6.5, 20% glycerol for a time sufficient for cystal development.

25. The method of claim 24, further comprising optimizing said crystallization condition.

26. The method of claim 24, wherein said crystallization condition comprises approximately 8% polyethylene glycol (PEG) 8000.

27. The method of claim 24, wherein said PYK2 is seleno-methionine labeled PYK2.

28. A co-crystal of PYK2 and a PYK2 binding compound.

29. The co-crystal of claim 28, wherein said binding compound interacts with at least one of PYK2 residues 503, 505, 457, 488, 567, and 554.

30. The co-crystal of claim 28, wherein said binding compound has a chemical structure of Formula I.

31. The co-crystal of claim 28, wherein said co-crystal is in an X-ray beam.

32. A method for obtaining co-crystals of PYK2 with a binding compound, comprising subjecting PYK2 protein at 5-20 mg/ml to crystallization conditions 2-10 % polyethylene glycol (PEG) 8000, 0.2 M sodium acetate, 0.1% sodium cacodylate pH 6.5, 20% glycerol in the presence of binding compound for a time sufficient for cystal development.

33. The method of claim 32, wherein said binding compound is added to said protein to a final concentration of 0.5 to 1.0 mM.

34. The method of claim 32, wherein said binding compound is in a dimethyl sulfoxide solution.

35. The method of claim 32, wherein said crystallization condition comprise approximately 8 % polyethylene glycol (PEG) 8000.

36. A method for determining a structure of a kinase, comprising

creating a homology model from an electronic representation of a PYK2 structure.

37. The method of claim 36, wherein said creating comprises

identifying conserved amino acid residues between PYK2 and said kinase;

transferring the atomic coordinates of a plurality of conserved amino acids in said PYK2 structure to the corresponding amino acids of said kinase to provide a rough structure of said kinase; and

constructing structures representing the remainder of said kinase using electronic representations of the structures of the remaining amino acid residues in said kinase.

38. The method of claim 37, further comprising fitting said homology model to low resolution x-ray diffraction data from one or more crystals of said kinase.

39. The method of claim 37, wherein the coordinates of conserved residues from Table 3 are utilized.

40. The method of claim 37, wherein coordinates of conserved residues from a mutated PYK2 are utilized.

41. An electronic representation of a crystal structure of PYK2.

42. The electronic representation of claim 41, containing atomic coordinate representations corresponding to the coordinates listed in Table 1 or Table 2.

43. The electronic representation of claim 41, comprising a schematic representation.

44. The electronic representation of claim 41, wherein atomic coordinates for a mutated PYK2 are utilized.

45. The electronic representation of claim 44, wherein said PYK2 consists essentially of a PYK2 kinase domain.

46. An electronic representation of a binding site of PYK2.

47. The electronic representation of claim 46, comprising representations of PYK2 residues 503, 505, 457, 488, 567, and 554.

48. The electronic representation of claim 46, comprising a binding site surface contour.

49. The electronic representation of claim 46, comprising representations of the binding character of a plurality of conserved amino acid residues.

50. The electronic representation of claim 46, further comprising an electronic representation of a binding compound in a binding site of PYK2.

51. The electronic representation of claim 46, wherein said PYK2 is a mutated PYK2.

52. An electronic representation of a PYK2 based homology model for a kinase.

53. The electronic representation of claim 52, wherein said homology model utilizes conserved residue atomic coordinates of Table 1 or Table 2.

54. The electronic representation of claim 52, wherein atomic coordinates for a mutated PYK2 are utilized.

55. A method for identifying a ligand binding to PYK2, comprising

determining whether a derivative compound that includes a core structure of Formula I binds to PYK2 with altered binding affinity or specificity or both as compared to the parent compound.

56. A method for modulating PYK2 activity, comprising

contacting PYK2 with a compound that binds to PYK2 and interacts with three or more of residues 503, 505, 457, 488, 567, and 554.

57. The method of claim 56, wherein said compound is a compound of Formula I.

58. The method of claim 56, wherein said compound is at a concentration of 200 μM or less.

59. A method for treating a patient suffering from a disease or condition characterized by abnormal PYK2 activity, comprising

administering to said patient a compound that interacts with three or more of PYK2 residues 503, 505, 457, 488, 567, and 554.

60. The method of claim 59, wherein said compound is a compound of Formula I.

61. The method of claim 59 wherein said disease or condition is a cancer.

62. The method of claim 59, wherein said disease or condition is an inflammatory disease or condition.

63. The method of claim 59, wherein said compound interacts with residues 503 and 505.

64. An electronic representation of a modified PYK2 crystal structure, comprising

an electronic representation of the atomic coordinates of a modified PYK2.

65. The electronic representation of claim 64, wherein said modified PYK2 comprises a C-terminal deletion, an N-terminal deletion or both.

66. A method for developing a biological agent, comprising

analyzing a PYK2 crystal structure and identifying at least one sub-structure for forming a said biological agent.

67. The method of claim 66, wherein said substructure comprises an epitope, and said method further comprises developing antibodies against said epitope.

68. The method of claim 66, wherein said sub-structure comprises a mutation site expected to provide altered activity, and said method further comprises creating a mutation at said site thereby providing a modified PYK2.

69. The method of claim 66, wherein said sub-structure comprises an attachment point for attaching a separate moiety.

70. The method of claim 69, wherein said separate moiety is selected from the group consisting of a peptide, a polypeptide, a solid phase material, a linker, and a label.

71. The method of claim 69, further comprising attaching said separate moiety.

72. A method for identifying potential PYK2 binding compounds, comprising

fitting at least one electronic representation of a compound in an electronic representation of a PYK2 binding site.

73. The method of claim 72, wherein said electronic representation of a PYK2 binding site is defined by atomic structural coordinates set forth in Table 1 or Table 2.

74. The method of claim 73, comprising

removing a computer representation of a compound complexed with PYK2 and fitting a computer representation of a compound from a computer database with a computer representation of the active site of PYK2; and

identifying compounds that best fit said active site based on favorable geometric fit and energetically favorable complementary interactions as potential binding compounds.

75. The method of claim 73, comprising

modifying a computer representation of a compound complexed with PYK2 by the deletion or addition or both of one or more chemical groups;

fitting a computer representation of a compound from a computer database with a computer representation of the active site of PYK2; and

identifying compounds that best fit said active site based on favorable geometric fit and energetically favorable complementary interactions as potential binding compounds.

76. The method of claim 73, comprising

removing a computer representation of a compound complexed with PYK2 and; and

searching a database for compounds having structural similarity to said compound using a compound searching computer program or replacing portions of said compound with similar chemical structures using a compound construction computer program.

77. The method of claim 73, wherein said compound is a compound of Formula I.

78. The method of claim 82, wherein said fitting comprises determining whether a said compound will interact with one or more of PYK2 residues 503, 505, 457, 488, 567, and 554.

79. A method for attaching a PYK2 binding compound to an attachment component, comprising

identifying energetically allowed sites for attachment of a said attachment component on a kinase binding compound; and

attaching said compound or derivative thereof to said attachment component at said energetically allowed site.

80. The method of claim 79, wherein said attachment component is a linker for attachement to a solid phase medium, and said method further comprises attaching said compound or derivative to a solid phase medium through a linker attached at a said energetically allowed site.

81. The method of claim 79, wherein said kinase comprises conserved residues matching at least one of PYK2 residues 503, 505, 457, 488, 567, and 554.

82. The method of claim 80, wherein said linker is a traceless linker.

83. The method of claim 80, wherein said kinase binding compound or derivative thereof is synthesized on a said linker attached to said solid phase medium.

84. The method of claim 83, wherein a plurality of said compounds or derivatives are synthesized in combinatorial synthesis.

85. The method of claim 80, wherein attachment of said compound to said solid phase medium provides an affinity medium.

86. The method of claim 79, wherein said attachment component comprises a label.

87. The method of claim 86, wherein said label comprises a fluorophore.

88. A modified compound, comprising

a compound of Formula I, with a linker moiety attached thereto at an energetically allowed site for binding of said modified compound to PYK2.

89. The compound of claim 88, whereins said linker is attached to a solid phase.

90. The compound of claim 88, wherein said linker comprises or is attached to a label.

91. The compound of claim 88, wherein said linker is a traceless linker.

92. A method for developing a ligand for a kinase comprising conserved residues matching one or more of PYK2 residues residues 503, 505, 457, 488, 567, and 554, comprising

determining whether a compound of Formula I binds to said kinase and interacts with said residue.

93. The method of claim 92, wherein said kinase comprises conserved residues matching at least 2 of PYK2 residues 503, 505, 457, 488, 567, and 554.

94. The method of claim 92, wherein said kinase comprises conserved residues matching PYK2 residues 503, 505, 457, 488, 567, and 554.

95. The method of claim 92, further comprising determining whether said compound modulates said kinase.

96. The method of claim 92, wherein said determining comprises computer fitting said compound in a binding site of said kinase.

97. The method of claim 92, further comprising forming a co-crystal of said kinase and said compound.

98. The method of claim 97, further comprising determining the binding orientation of said compound with said kinase.